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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,204	02/11/2004	Craig A. Rosen	PF564	1797

22195 7590 11/26/2004

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EXAMINER	
WAX, ROBERT A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/775,204	ROSEN ET AL.	
	Examiner	Art Unit	
	Robert A. Wax	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) 19-21 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-18, drawn to fusion proteins and methods of their use, classified in class 514, subclass 12.

   II. Claims 19-21, drawn to nucleic acid molecules encoding the fusion proteins, vector and host cell containing them, classified in class 435, subclass 254.11.

The inventions are distinct, each from the other because of the following reasons:

2. The protein of group I is related to the nucleic acid of group II by virtue of the fact that the nucleic acid codes for the protein. The nucleic acid molecule has utility for the recombinant production of the protein in a host cell. Although the nucleic acid and the protein are related, since the nucleic acid encodes the specifically claimed protein, they are distinct inventions because the protein product can be made by other and materially distinct processes, such as chemically linking the fusion partners obtained by purification from the natural sources. Further, nucleic acid can be used for processes other than the production of protein, such as nucleic acid hybridization assays.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classifications and divergent searches and restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Michele Wales on November 15, 2004 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-18. Affirmation of this election must be made by applicant in replying to this Office action. Claims 19-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

6. The current application filed on February 11, 2004 is a continuation of PCT/US02/40891 filed on December 23, 2002, which in turn claims priority to many provisional applications, the earliest of which is 60/341,811 filed on December 21, 2001.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are rendered indefinite by the recitation of X and Y from Tables 1 and 3, respectively. Attention is directed to MPEP 2173.05(s), which states,

> Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

The instant case does not appear to be one of the "exceptional circumstances" to which the above paragraph refers.

The claims are also rendered indefinite by claim 1(m). It is clear what is meant by "inserted into an albumin" but the recitation of specific amino acids is not understood. Does the therapeutic protein replace the recited sequence? Is it inserted after the recited sequence? Or what?

The claims are also rendered indefinite by the recitation of "albumin activity". Albumin is well known to be a rather inert protein that is responsible for the osmotic pressure of the blood. Salvi et al. teach that HSA has esterase-like activity but that activity is clearly not contemplated in the instant specification. The property of enhancing the shelf life and serum half-life of proteins is not considered to be an

activity since the latter term implies that the albumin actually does something, like an enzyme has an activity.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

This rejection comprises two parts, the first of which is directed to the nonenablement of the variants of albumin and the second of which is directed to the nonenablement of the fragments and variants of the therapeutic proteins.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for full length HAS represented by SEQ ID NO: 1038 and fragments thereof, does not reasonably provide enablement for variants of SEQ ID NO: 1038. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

A number of factors must be considered in assessing the enablement of an invention, including the following: the breadth of the claims, the amount of experimentation necessary, the guidance provided in the specification, working examples provided, predictability, and the state of the art. See *In re Wands*, 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Circ. 1988).

In order for one skilled in the art to produce sequences that are "variants", one would have to either (a) randomly search natural living sources to locate any possible

sequence that was a "variant" or (b) mutate the known single sequence provided by applicants, by deletion, insertion or substitution of any number of the nucleotides. Therefore, the language of the claims encompasses an inordinate number of possible sequences. The specification does not provide direct guidance for any such mutations, nor does it provide one skilled in the art with guidance as to where one may attempt to locate other sequences that would be expected to be "variants". The level of skill in the art would have been such that the artisan could easily alter the codons in accordance with another preferred codon that encodes the same amino acid, without altering the primary structure of the protein, and therefore without altering the protein's activity. However, the claims are not so limited. The resultant effect of the random mutations encompassed by the claims would be highly unpredictable to one skilled in the art. It would require an undue amount of experimentation for one skilled in the art to attempt to produce the millions of possible various mutations such as insertions, deletions and substitutions of any type, amount or combination of nucleotides to produce the changes in the protein, and maintain a functional protein. For example, the mutation of any of the instant protein's amino acids, with a single substitution only, would create ($1x10^{585}$ - 1) possibilities alone. As little or no guidance is provided regarding these possible mutational events encompassed by the claims, and given that the selection, production and screening of such a large number would constitute an undue amount of experimentation, the variants are not enabled by the teachings of the specification.

The following paragraphs relate to the nonenablement of the fragments and variants of the therapeutic proteins. The factors that must be considered are outlined in the previous paragraph.

In order for one skilled in the art to produce sequences that are "variants" of the therapeutic proteins, one would have to either (a) randomly search natural living sources to locate any possible sequence that was a "variant" or (b) mutate the known single sequence provided by applicant, by deletion, insertion or substitution of any number of the nucleotides. Therefore, the language of the claims encompasses an inordinate number of possible sequences. This is exacerbated by the large number of therapeutic proteins encompassed within the claims. The specification does not provide direct guidance for any such mutations, nor does it provide one skilled in the art with guidance as to where one may attempt to locate other sequences which would be expected to be "variants". The level of skill in the art would have been such that the artisan could easily alter the codons in accordance with another preferred codon that encodes the same amino acid, without altering the primary structure of the protein, and therefore without altering the protein's activity. However, the claims are not so limited. The resultant effect of the random mutations encompassed by the claims would be highly unpredictable to one skilled in the art. It would require an undue amount of experimentation for one skilled in the art to attempt to produce the millions of possible various mutations such as insertions, deletions and substitutions of any type, amount or combination of nucleotides to produce the changes in the protein, and maintain a functional protein. As no guidance is provided regarding these possible mutational

events encompassed by the claims, and given that the selection, production and screening of such a large number would constitute an undue amount of experimentation, the variants of the therapeutic proteins recited in the claims would not be enabled by the teachings of the specification.

Further, applicants have not provided sufficient guidance toward the production of various "fragments" of the instant protein, of any length, content or function. Initially, this reads upon a single amino acid, all the way up to a near full-length molecule. Applicants have not provided guidelines concerning the proper protocol for producing such fragments; for the selection of size, content, location in the molecule; or for screening and assaying for function, if any. Nor have applicants provided working examples as guidance in this matter. Thus, absent these necessary teachings, it would require an undue amount of experimentation for one skilled in the art to randomly and blindly attempt to produce any type of fragment of the disclosed protein, and the path to successfully producing such would be highly unpredictable. Thus, the fragments of the therapeutic proteins are not enabled.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-4, 6 and 11-18 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Delta Biotechnology (WO 97/24445).

Delta Biotechnology teaches fusion proteins of human growth hormone and albumin, expressed preferentially in yeast, which exhibit enhanced storage stability and serum half-life. Treatment methods are taught in claim 19, administration of the polypeptide must be in some kind of pharmaceutical composition; this anticipates claims 12-17. Claims 4 and 5 are included because the fusions of Delta Biotechnology must inherently display the recited properties since they are the same compounds and the properties of the compound are not divisible from the compound.

12. Claims 1-6 and 9-17 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Fleer et al.

Fleer et al. teach fusion polypeptides between therapeutic proteins and albumin exhibiting enhanced shelf life and serum half-life. The fusions may be made in several different patterns, including an optional linker, which read on those delineated in instant claim 1, parts a-k, n and o. Increased in vitro activity is taught for von Willebrand factor fusions with albumin at column 22, lines 25-30; this implies that the fused vWF would also inherently have increased in vivo activity. Although the preferred host cell in which to make the fusion proteins is yeast (thus, instant claim 6 is anticipated), claim 11 teaches expression in mammalian cells as well as bacteria; this anticipates instant

claims 5, 9 and 10. The presence of a secretion leader sequence is taught at column 11, lines 8-9, thus anticipating instant claim 11. Pharmaceutical compositions and, by extension, kits and methods of treatment, are taught in claim 15 and at column 1, lines 33-35, for example. Thus, these teachings anticipate the above claims.

13. Claims 1-4 and 14-16 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Human Genome Sciences (WO 02/097038 A3).

HGS teaches fusion proteins with ckbeta1 and albumin. Claims 4-7 in the reference track instant claim 1 and the properties claimed in instant claims 2-4 are taught in the specification. Claim 15 in the reference tracks instant claims 14-16, thus, it is considered that HGS clearly anticipates the instant claims.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

14. Claims 1-18 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Human Genome Sciences (WO 03/030821 A2).

HGS teaches fusion proteins with human growth hormone and albumin and, since the claims in the reference track the instant claims, it is considered that HGS clearly anticipates the instant claims.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

15. Claims 1-18 are also rejected under 35 U.S.C. 102(e) as being clearly anticipated by Human Genome Sciences (US 2003/0171267 A1).

HGS teaches fusion proteins with albumin and the following proteins, all found in instant Table 1: calcitonin (page 27 of the specification), growth hormone releasing factor (ghrf) (pages 31-32), interferon β (pages 28-29), IL-2 (pages 32-33) and parathyroid (page 34). These proteins are taught in claim 59 of the reference. Since the claims in the reference track the instant claims, it is considered that HGS clearly anticipates the instant claims.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Double Patenting

16. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

17. Claims 1-18 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-26 and 60-71 of copending Application No. 09/833,117. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

18. Claims 1-18 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-26 of copending Application No. 10/816,042. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

19. Claim 1 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 4-7 and claims 14-16 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 15 of copending Application No. 10/153,604. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

20. Claims 1-18 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-29 of copending Application No. 10/775,180. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

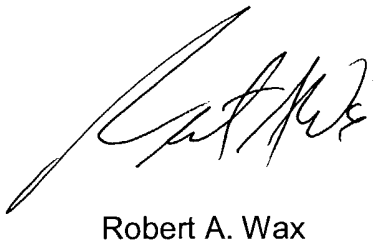
Conclusion

21. No claim is allowed. Spencer et al., Lok et al. and Kieke et al. are cited since they were cited in the International Search Report. No rejection was made over Spencer et al. since they teach only Bovine Serum Albumin. The other teachings were cumulative to the teachings of the references that were used in rejections.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday, between 9:00 AM and 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Robert A. Wax
Primary Examiner
Art Unit 1653

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